REMARKS

1. Restriction Requirement

In the Restriction Requirement mailed September 28, 2006 the Examiner alleges that "clams 1, 6, 33 and 37 are generic to a plurality of disclosed patentably distinct species comprising the bovine traits of marbling, tenderness, quality grade, muscle content, fat thickness, feed efficiency, red meat yield, average daily weight gain, disease resistance, disease susceptibility, feed intake, protein content, bone content, maintenance energy requirement, mature size, amino acid profile, fatty acid profile, milk production, a milk quality susceptibility to the buller syndrome, stress susceptibility and response, temperament, digestive capacity, production of calpain, caplastatin and myostatin, pattern of fat deposition, ribeye area, ovulation rate, conception rate, fertility, and susceptibility to infection with and shedding of pathogens." Office Action at p. 2. Election of a single disclosed species has been required. *Id.*

In addition, the Examiner alleges that there are "42,904 patently distinct inventions," corresponding to "individual SEQ ID Nos. 19473-21982 and 24493-64886." *Id.* The Examiner states that "Applicant is required to elect a single SNP sequence from the group of the SEQ ID NOS 19473-21982, and to elect a single oligonucleotide sequence from the group of the SEQ ID NOS 24493-64886. This is not a species election." *Id.* In support of the restriction requirement, the Office Action states that "sequence searching in multiple expansive databases has put undue burden on the examiner and office resources." *Id.*

2. Election

A. In order to be fully responsive to the restriction requirement, Applicants provisionally elect the trait of a bovine subject of tenderness as a species of generic claims 1, 6, 33 and 37, with traverse.

Applicants note that 37 CFR §1.141 provides that an allowable generic claim may link a reasonable number of species embraced thereby. *See* 37 CFR §§1.141, 1.146; MPEP 806.04. Applicants reserve the right to examination of a reasonable number of species in addition to the one elected for examination purposes when the generic claims 1, 6, 33 and 37 are found allowable. *See* MPEP 821.04(a).

B. Applicants further elect the single nucleotide polymorphism (SNP) of marker MMBT05224 as set forth in SEQ ID NO:21645, and the extension primer set forth in SEQ ID NO: 24155, with traverse.

3. Traversal

The Office Action alleges that the above-identified application contains 42,904 inventions and Applicants have been required to elect one of the alleged inventions for examination.

In support of the restriction requirement, the Examiner stated, without further explanation or citation to legal authority, that the sequences of the invention are "patently distinct inventions." Office Action at p. 2. However, the restriction requirement was justified largely on the basis of search burden. Specifically, the Examiner stated "sequence searching in multiple

expansive databases has put undue burden on the examiner and office resources." *Id.* While this is an important consideration, it is well established that search burden alone is insufficient grounds for restriction.

In addition, the "inventions" sought to be restricted must be shown to be **independent** or **distinct** ***as claimed.*** Thus, the basic requirement for a proper Restriction requirement is two-fold. *See* MPEP 803.I. First, the alleged inventions must be independent or distinct as claimed. *Id.* Second, there must be a serious burden on the Examiner if restriction is not required. *Id.* Nevertheless, the courts and Patent Office have also recognized "an applicant's right to define what he regards as his invention as he chooses." *See, e.g., In re Harnisch*, 206 U.S.P.Q. 300, 305 (CCPA 1980).

The Patent Office has determined that nucleic acid sequences "***that encode different proteins*** are structurally distinct chemical compounds." MPEP 803.04. This determination forms the basis for presuming that each polynucleotide sequence recited in a claim is an independent and distinct invention. Applicants do not dispute this presumption as it applies to nucleic acid sequences that have been shown to encode a protein. However, it is well known that the vast majority of a mammalian genome is comprised of non-coding regions. Within the genome, there are sequences, commonly referred to as "markers," that simply provide a reference point on a chromosome.[1] Markers can, but need not be, located in a nucleic acid

[1] The definition of a "marker" is: "An identifiable physical location on a chromosome (for example, restriction enzyme cutting site, gene) whose inheritance can be monitored. Markers can be expressed regions of DNA (genes) or some segment of DNA with no known coding function but whose pattern of inheritance can be determined." *See* http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=marker&action=Search+OMD, a copy of which is attached hereto as Exhibit A.

sequence that encodes a protein. *See* specification at 28, [0072]. Moreover, their function as a ***marker*** is not dependent on, and is typically separate from, whether the sequence resides in a protein-encoding sequence or not. Indeed, their function is to ***locate*** sequences that encode proteins and to facilitate the ***association of genes*** with phenotypic traits, which may be complex and involve many encoded proteins and genes. If the relationship between a particular sequence that encodes a protein and the phenotypic trait were known, there would be no need for markers.

Single nucleotide polymorphisms are markers for a particular location on the chromosome that can be used to identify genes and correlate traits. As a group, they have no known protein-encoding function. They simply represent a difference that is observed at a single nucleotide position on a chromosome. In virtually all instances, there are only two forms of the SNP. Because of this difference, molecular geneticists can map traits to certain regions of a chromosome by association with one variety of the SNP or another, and thereafter, use the association information to predict whether an animal [or human] will have the trait.

The significance of SNPs is ***not*** related to whether one SNP is present in a nucleic acid sequence that encodes a particular protein and a different SNP is present in a nucleic acid sequence that ***encodes a different protein***. Indeed, if the causative relationship between a SNP

Merriam-Webster's online Medical dictionary provides the following definition of "marker": "something that serves to identify, predict, or characterize." *See* http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=marker, a copy of which is attached hereto as Exhibit B.

The same dictionary further specifies that at genetic marker is
"a readily recognizable genetic trait, gene, DNA segment, or gene product used for identification purposes especially when closely linked to a trait or to genetic material that is difficult to identify -- called also marker" *See* http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=genetic+marker, a copy of which is attached hereto as Exhibit C.

and the difference in proteins that leads to a phenotypic trait were clearly understood, it would not be necessary to use SNPs as markers. One could go straight to the known causative differences between proteins or the nucleic acid sequences that encode them to infer a phenotypic trait. In quantitative genetic approaches using SNPs, the genes and "genetic architecture of the trait itself is treated as a black box, with no knowledge of the number of genes that affect the trait, let alone of the effects of each gene or their locations in the genome." *See e.g.,* Dekkers & Hospital, Nature Rev. Genetics 3:22-32, 22 (2002), a copy of which is attached hereto as Exhibit D. This type of analysis is based on "Fisher's infinitesimal genetic mode, in which the trait is assumed to be determined by an infinite number of genes, each with a infinitesimally small effect [on the trait]." *Id.*

Accordingly, applicants submit that the fundamental assumptions under which the Patent Office has made a presumptive determination that each nucleic acid sequence is an independent and distinct invention do not apply to SNPs, particularly the SNPs claimed in claims 1-28 and 33-38.

As discussed above, SNPs functioning as markers identify a particular position on a chromosome – a point of reference. Unfortunately, the nature of the genome combined with Patent Office rules do not allow this single point of reference to be expressed in the absence of the surrounding sequence information. A SNP, as recited in claims 1-28 and 33-38 is in fact a single point – not a gene or a protein-encoding nucleic acid. However, the limitations of the art of molecular biology requires that a sufficient amount of nucleic acid sequence information flanking that single point is recited in order to uniquely identify the single point. Furthermore,

the Patent Office requires that nucleic acid sequences be expressed by SEQ ID NOs, as described in MPEP 2421-2425.

Nevertheless, the essential information represented by a SNP as recited in claims 1-28 and 33-38 is simply a single nucleotide polymorphism which identifies or marks a single point on a chromosome.

Applicants submit that the SNPs recited in claims 1-28 and 33-38 are not independent and distinct inventions as claimed and respectfully request reconsideration and withdrawal of the restriction requirement.

The SNPS of the Present Invention are Not Independent

According to the MPEP, "[i]nventions as claimed are independent if there is no disclosed relationship between the inventions, that is, they are unconnected in design, operation, and effect." MPEP 806.06. Applicants submit that the SNPs as recited in claims 1-28 and 33-38 are intimately connected in design, operation and effect.

As points of reference on a chromosome, SNPs permit the ability to associate a region or position of the chromosome with a trait of interest. Such mapping requires a multitude of SNPs at various positions on the chromosome. *See e.g.,* specification at p. 8. [0021]. Locating a trait of interest having an unknown location would not be possible if only a single point of reference were available in the genome. *Id.* The skilled artisan requires multiple points along each of the chromosomes of an animal in order to locate a gene. *See e.g.*, specification at Example 2, p. 60.

However, given a large pool of SNPs or reference points, no individual points is *a priori* more effective than another for locating a gene or genes contributing to a trait. Furthermore, SNPs that are sufficiently close to each other are essentially interchangeable because they mark the same approximate location on the chromosome. *See* specification at p. 13, [0035].

Once a group of SNPs has been associated with an individual trait, groups of SNPs are similarly connected in design, operation, and effect. Furthermore, the skilled artisan will appreciate that use of only one, individual SNP to infer a trait is limited. *See, e.g.*, Andersson & Georges, *Nature Rev. Genetics*, 5:202-212 (2004), a copy of which is attached hereto as Exhibit E. For example, in order to be able to track meat of a bovine subject, a series of SNPs is required. *See* Specification at p. 32, [0103] to p. 33, [0106]. Although a inference can be made using a single SNP associated with the trait, unless that SNP identifies a causative mutation in a gene solely responsible for determining the trait, the inference that can be made is often only partially predictive. Thus a strong inference typically requires the identification of multiple SNPs. *See* specification at p. 19, [0058].

At the same time, however, any two SNPs associated with a trait may be functionally interchangeable or identical for the purpose of making an inference. SNPs that are located in close proximity to each other can be essentially interchangeable in ability to infer a trait by association. Furthermore, the actual number of SNPs that must be used to infer a trait is not fixed, but rather relates to the degree or strength of the inference that can be made; the more SNPs or points that are used to make the inference, the greater the statistical significance of that inference. Specification at p. 19, [0058].

In the case of tenderness, multiple SNPs were identified across the genome that are correlated to the tenderness trait. *See* specification at p. 61-62; Tables 1A and 1B. It is likely that many of the SNPs associated with tenderness are functionally interchangeable, yet at the same time, the most accurate prediction regarding the trait will require detection of a plurality of SNPs.

The SNPS of the Present Invention are Not Distinct

Similarly, Applicants submit that the SNPs as recited in claims 1-28 and 33-38 are not distinct inventions as claimed. The test for distinct inventions, as set forth in the MPEP, is:

> inventions are distinct if
>
> (A) the inventions as claimed do not overlap in scope, i.e., are mutually exclusive;
>
> (B) the inventions as claimed are not obvious variants; and
>
> (C) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect.

See MPEP 806.05(c).

Applicants submit that the SNPs as recited in claims 1-28 and 33-38 fail to meet at least elements (A) and (C) of the test for distinctness, and therefore are not distinct inventions. Regarding element (A) the SNPs of the claimed invention overlap in scope. As discussed above, any two closely spaced SNPs may be interchanged with respect to mapping, and frequently are interchangeable for trait inference. Simply put, one point is typically as good as another, provided enough points are available. When the use of the SNP is for a particular trait inference, the more SNPs associated with the trait, the better. Yet within a group of SNPs that are informative or associated with a trait, particular subsets or individual SNPs may not be superior

to others. Indeed, either of two or more closely linked SNPs can be used to infer a trait, yet the inference will be stronger if a third or fourth or fifth SNP is also determined. Specification at p. 19, [0058]. Furthermore, when a trait is polygenic and/or when epistasis is involved in the phenotypic expression of the trait (as recited in claim 4), multiple SNPs are absolutely required to make an appropriate inference. Specification at p. 34, [0113] to p. 35, [0115]. Thus, Applicants submit that the SNPs recited in claims 1-28 and 33-38 are not mutually exclusive and therefore fail to meet element (A) of the test for distinct inventions.

Regarding element (C) of the test for distinctness, the SNPs of claims 1-28 and 33-38 clearly are capable of use together as discussed in the preceding paragraphs. Furthermore, they ***must*** be used together for trait mapping and in most applications of trait inference, particularly where epistasis is involved or the trait is polygenic. In addition, the SNPs of claims 1-28 and 33-38 share the same design, operation, function and effect – they simply represent points on the chromosome and although each SNP represents a specific point, in the context of their role ***as claimed***, each functions to facilitate gene mapping and trait inference by marking that particular point to the same effect as any other SNP. Thus, Applicants submit that the SNPs as recited in claims 1-28 and 33-38 fail to meet element (C) of the test for distinct inventions, and therefore are not distinct. *See also*, MPEP 806 (C) ("Where inventions are related as disclosed but are not distinct as claimed, restriction is never proper.").

Taken together, Applicants submit that the SNPs as recited in claims 1-28 and 33-38 are neither distinct nor independent inventions. Accordingly, restriction to a single SNP is improper under MPEP 803 (stating that "[u]nder the statute, the claims of an application may properly be

required to be restricted...only if they are...are either independent or distinct.") (citations omitted).

Accordingly, Applicants respectfully request reconsideration and withdrawal of the Restriction Requirement.

Applicants are Entitled to Claim a Reasonable Number of at Least Ten (10) Sequences

Notwithstanding Applicants' submissions above supporting the lack of independence of distinctiveness of the claimed sequences, the Director "has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application." Specifically, the MPEP states that "ten sequences constitute a reasonable number for examination purposes...[that] will be examined in a single application without restriction."

Applicants submit that regarding claims 1-28 and 33-38 a minimum of 10 sequences selected from the group of recited sequences constitute a reasonable number of sequences for examination purpose according to the MPEP.

Accordingly, reconsideration and withdrawal of the Restriction Requirement is respectfully requested.

The Restriction Requirement as Applied to the Recited Markush Groups is Improper.

According to the MPEP, "members of [a] Markush group ... ordinarily must belong to a recognized physical or chemical class or to an art-recognized class." MPEP 803.02. When such

a Markush group is present, it is improper to restrict individual members of the group. *Id.* Furthermore, the MPEP instructs that "when the Markush group occurs in a claim reciting ***a process*** or a combination (not a single compound), it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is mainly responsible for their function in the claimed relationship, and it is clear from their very nature or from the prior art that all of them possess this property." MPEP 803.02.

Applicants submit that the SNPs of claims 1-28 and 33-38 are all from the same recognized class. Furthermore, these SNPs share the property disclosed in the specification, particularly in Tables 1A and 1B, of a demonstrated association with commercially important bovine traits. Accordingly, it is improper to restrict the claims 1-28 and 33-38 on the basis of the SNPs when the SNPs are members of a recognized class and share a common property where the Markush group recited in a method claim rather than a composition claim.

Moreover, even if the SNPs are determined to be unrelated by class or property, the MPEP has a separate subsection that deals particularly with "Markush-type generic claims which recite a plurality of alternatively usable substances or members." *Id.* According to the MPEP, this section applies to the type of claims that contain "a recitation by enumeration...because there is no appropriate or true generic language," that can substitute for the recitation. *Id.* These Markush-type claims "***may include independent and distinct inventions***" including claims where "two or more of the members [of the Markush group] are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s)." *Id.* (emphasis added).

Applicants submit that the SNPs are either related by class and/or property, or are unrelated. In either case, as members of a Markush group, particularly in a method claim, outright restriction is improper.

The procedure for these types of claims does not include immediate, outright restriction of the Markush group to individual members. Instead, the Examiner is directed that

> [i]f the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions.

Id.

In the event that the examination of the members of a Markush group is considered to be a serious burden, then the Examiner is permitted to "require a ***provisional*** election of a single species prior to examination on the merits." *Id.* (emphasis added). "Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability." Only after examination and a finding that the "Markush-type claim is not allowable over the prior art," can the restriction be applied with respect to the elected species. Upon such a finding, "the provisional election will be given effect and examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration." *Id.*

Applicants submit that to the extent that the single-nucleotide polymorphisms and extension primers recited in Markush form in claims 1-28 and 33-38 are held to be independent

and distinct inventions, the outright restriction of each member of the Markush group is improper.

Applicants submit that the proper procedure in this case is to first determine whether the entire group can be examined without undue burden, and to do so where possible. If this is not possible, then the proper procedure is to require a ***provisional*** election of one species of the genus by enumeration of claim 1-28 and 33-38 for examination on the merits, subject to continued examination of a reasonable number of species upon finding the elected species patentable.

Accordingly, Applicant respectfully request that if the restriction requirement is not withdrawn *in toto*, then the elections made by the present response are treated as an election of species for initial search and examination and that the once the claims reading on the elected species are found patentable, the search and examination is continued for a reasonable number of species.

Check number 6506668 in the amount of $120.00 is enclosed for the One-Month Extension of Time fee. No other fee is deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees that are required, or credit any overpayments to Deposit Account No. 07 1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

Date: November 28, 2006

Lisa A. Haile, J.D., Ph.D.
Registration No.: 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No.: 28213